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EPIDEMIOLOGICAL SURVEILLANCE OF INFLUENZA AND OTHER RESPIRATORY DISEASES IN MILITARY PERSONNEL

PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES - LABORATORY STUDIES

ANNUAL REPORT

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1. Further HI tests with sera from patients who had Influenza B in 1986 and 1987 using B/Ann Arbor/86 or B/Denver/2/86 whole virus antigens showed that a titer of 32 was protective.

2. Monovalent A/Taiwan/86 vaccine produced a remarkably good response of homologous HI antibody in recruits who had previously received standard vaccine that contained A/Chile/83 as its H1N1 component.

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Abstract (continued)

3. The HI antibody response of recruits, permanent party and retirement home residents in San Antonio were determined using two Influenza A H3N2, two H1N1 and one Influenza B antigens. Responses were by far the best in recruits, somewhat less satisfactory in the permanent party and even less in the retirement home residents. It appeared that influenza had occurred in the recruit population between the two bleedings, giving a false impression of an exceptional A/Taiwan/86 response to the Chile component of the vaccine.

4. Influenza A H1N1 began to occur during the middle of November and continued to the middle of February. The attack rate in students was 1.2% and in the permanent party somewhat higher. However, when only the Lowry Base personnel who had been vaccinated were counted, the rates in the permanent party were essentially the same as in the students.

5. The highest febrile URI rate observed in Air Force students was 7.2/1000/week.

6. The protective HI antibody level in students was 32. In the permanent party this was less clearly defined, with a few individuals with influenza having HI titers of 64 or 128.

7. Fifty-seven of 68 cases of influenza occurred in members of the permanent party between the ages of 18 and 30. Only three cases were found in individuals between 36 and 40 years of age, and none were found among individuals over 41.

8. Comparison of A/Taiwan/86 HI titers of students bled before and after the influenza outbreak indicated that inapparent infection had occurred in approximately 20% of the student population. A similar study of sera collected from the permanent party failed to show a similar spread of infection.

9. The HI test using whole virus A/Taiwan/86 antigen was the best diagnostic procedure (86%). Virus was isolated from 66%. Complement fixation tests were positive in 61%.

10. Influenza A was responsible for 32.6% of febrile URIs throughout the winter; streptococcal pharyngitis 13.5%; the remaining 54% continued to be of unknown etiology. Testing of over 200 serum pairs with chlamydia TWAR antigen disclosed only one case with a significant rise in CF antibody titer.

11. The current military vaccine appears to have protected students well during recent outbreaks caused by Influenza A of either H3N2 or H1N1 types and Influenza B.

12. Protection in the permanent party has been less satisfactory and further efforts should be made to develop a vaccine which would be more effective in this population.

FORWARD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

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INTRODUCTION

The last annual report covering the period through 30 June 1986 left unanswered the question of why the vaccine apparently had been less effective during the Influenza B outbreak than in previous years. Studies were completed during the summer months which showed that when the sera of vaccinated individuals were tested against strains isolated from the Lowry outbreak or against B/Ann Arbor/86 virus, the protective level of antibody was clearly demonstrated to be 32. This was not made clear when sera were tested with ether split B/USSR/83.

The 1986-87 season was notable for a sharp outbreak of H1N1 Influenza A, which began before the Christmas break, probably reached a peak during the Christmas holiday, and tailed off during January, with the last case detected during mid-February. Again it was found that the H1N1 virus caused very little illness in individuals over the age of 35. Attack rates in students were difficult to estimate because the outbreak appeared to be peaking at the time the students took a two-week Christmas break. In the permanent party, which for the most part remained on the Base over the Christmas holiday, attack rates were relatively high in the younger segment of that population.

No Influenza B viruses were isolated during this season. Influenza A of the H3N2 subtype was isolated from two civilians during this period but none were found at Lowry Air Force Base. In the civilian population the virus appeared to spread very poorly, in each case causing a cluster of only two or three other identified illnesses.

COMPLETION OF INFLUENZA B STUDIES FOR THE 1986-86 SEASON

The vaccine used during this season had contained the Influenza B/USSR/83 strain and when tests were done to determine H.I. antibody response, an ether split antigen had been used in order to obtain sufficiently high titers because of the lower avidity of the virus. The B/Ann Arbor/85 virus and two isolates from Lowry Air Force Base, namely Denver/1/86 and Denver/2/86, appeared to have reasonable avidity (Table 1), and serum from all patients were rerun using these antigens with B/USSR/83 ether split antigen. The results were quite different.

The tests with ether split B/USSR antigen had showed a relatively poor correlation between antibody titer and protection against illness, particularly in the permanent party where 10 of 68 cases occurred in persons with titers $\geq$128. With each of the three newly isolated strains, the protective titer appeared to be quite sharp at 32 (Table 2). This table also shows that, in the permanent party, relatively few individuals (28%) had titers $\geq$128. In the student population the corresponding figure was 72%. This corresponded with the fact that the rate of illness in the students was considerably lower than in the permanent party.

The antigens used in the tests shown in Tables 1-3 were different. The ether split and the B/USSR/83 antigen were provided by the CDC. The B/Ann Arbor/1/86 antigen was whole virus in the 8th egg passage. B/Denver/2/86 was tissue culture fluid from the second tissue culture passage in RMK. B/Denver/2/86 had come from a patient at Lowry Air Force Base along with two other B strains from the Denver area during the past winter. All were essentially non-avid in their early egg passages.

The data in Table 3 illustrate the confusion which may be encountered with the use of ether split antigens in HI tests. With ether split B antigen, it appeared that the antibody levels in both permanent party and students were reasonably good. Post-vaccination titers were $\geq$32 in 80% of the permanent party and 96% of the students. All but one person had titers $\geq$16. With B/Ann Arbor and B/Denver/86, the titers were far lower and the percent with titers $\geq$32 were extremely low. A very large proportion of individuals continued to have titers $\leq$8, suggesting that there was a large highly susceptible pool. It is impossible to separate what part of the difference is due to exaggerated response to the ether split antigen, to the low avidity of 1986 B strains, or due to antigenic drift.

MONOVALENT H1N1 A/TAIWAN/86 VACCINE

The standard vaccine prepared for the 1986-87 season contained as its H1N1 component the A/Chile/83 strain. During the preceding season a number of strains were isolated which showed considerable antigenic drift, and the recommendation of the Office of Biologics, National Center for Drugs and Biologics, FDA, was that a supplementary monovalent vaccine should be prepared for high risk individuals from strain A/Taiwan/86. To determine the situation in the Armed Services, 25 pairs of permanent party individuals at Lackland who were vaccinated in the fall of 1985 with H1N1 antigens A/Chile/83 along with the post-vaccination serum of 24 students were obtained. No prevaccination sera was available with A/Chile/83 from students during this season. The results are shown in Table 4.

In the permanent party 52% had prevaccination titers $\geq$32 for A/Chile/83; this percent increased only to 72% following vaccination. Only 8% of individuals showed titer increases $\geq$ 4-fold. The students showed considerably higher post-vaccination titers with 96% having titers $\geq$32. The results were very different with the A/Taiwan/86 virus and indicate considerably antigenic drift. The permanent party showed virtually no change in titer following vaccination and in the student population only 37% had titers $\geq$32. These data appeared to support the recommendation that a monovalent A/Taiwan/86 vaccine be added to the vaccine regimen.

When it appeared the monovalent vaccine would not be available until December, 100 doses of A/Taiwan/86 vaccine were obtained from the Parke-Davis Company during late October. This was given to a group of students in one squadron at Lowry Air Force Base on 12 November. Post-vaccination sera were obtained on 2 December. All these individuals had received trivalent vaccine approximately two or three months earlier. In sharp contrast to the response to the A/Chile/83 vaccine, there was a very striking response to the A/Taiwan/86 virus following the booster injection (Table 5). There was, furthermore, an increase in A/Chile titer after the Taiwan booster. Thus, 95% of the students had titers of $\geq$64 and 92% had titers $\geq$128 following the booster injection. These data were forwarded to CDC with approval of Air Force administration and were published in the MMWR of January 8, 1987.

HI ANTIBODY RESPONSE TO STANDARD VACCINE

Through the efforts of Lt. Col. Martin Evans at Lackland Air Force Base, slightly more than 100 serum pairs were received from each of three groups: recruits, permanent party at Lackland, and residents of an Air Force retirement home. All had received ether split vaccine containing 15 mcg each of A/Mississippi/85, A/Chile/83 and B/Ann Arbor/86. To date, 75 pairs of each of these groups has been tested for HI antibody against A/Mississippi/85, A/Chile/83, A/Taiwan/86 and B/Ann Arbor/86. Fifty pairs were also tested against the H3N2 strain A/Leningrad/86, which is replacing A/Mississippi/85 as the H3N2 component in the coming year's vaccine.

Results are shown in Tables 6, 7 and 8. The data are somewhat difficult to interpret and for this reason the results are discussed mainly in terms of the change from pre- to post-vaccination titers of individuals who had titers <8 (most susceptible) and those with titers $\geq$32 ("protected"). It is reasonable to assume that when the number of individuals with titers <8 is reduced to 0 and the percent of individuals with titers of $\geq$32 is 95% or higher, the vaccine will provide a high degree of protection.

ANTIBODY RESPONSE IN RECRUITS (Table 6)

H3N2

A/Mississippi/85

The response to the A/Mississippi/85 component was extremely good. Twenty-seven percent of the recruits had titers <8 before vaccination; after vaccination, 0%. The percent of individuals with titers >32 went up from 44% to 99% following vaccination.

A/Leningrad/86

A sharp antigenic drift away from A/Mississippi/85 is shown in the prevaccination sera by the fact that the percentage of individuals with titers $\geq$32 was 44% with A/Mississippi/85 and only 18% with A/Leningrad/86. Nevertheless, after the injection of vaccine containing A/Mississippi/85, there was a good response to the A/Leningrad/86 virus. The percent of individuals with titers of <8 fell from 30% to 4% and the percent of individuals with titers $\geq$32 rose from 18% to 86%. Experience in the past six years suggests that recruits will be well protected if a virus like A/Leningrad/86 is prevalent during the coming season.

A/H1N1

A/Chile/83

The response to this virus was remarkably good. The percent of individuals with titers <8 fell from 24% to 1% and of those with titers $\geq$32 rose from 30% to 100%. Ninety-four percent had titers $\geq$256.

A/Taiwan/86

There were considerably more individuals with titers <8 to A/Taiwan (81%) than to A/Chile/83 (24%). The post-vaccination percentage of individuals with titers >32 was 79% compared to 1% in the prevaccination sera. The degree of drift appears to be greater than with the H3N2 viruses.

This response rate is in definite conflict with the results in recruits who had been tested at Lowry earlier (Tables 4 and 5). These individuals had been vaccinated and bled at a time when there was no evidence of H1N1 in the community and presumably represented a valid response and indicated approximately 25% of the recruits had titers <8 following vaccination. The two tests checked well with each other.

It is noted in Table 6 that the second blood from these recruits was not collected until 2 December. It was noted by Lt. Col. Evans that there was an excess of influenza-like illness in recruits during the latter part of November and several H1N1 virus strains were isolated during this period. It is assumed consequently that the data represent not only the response to vaccine but also response to illness which apparently was fairly extensive during that period. These findings imply that more than 20% of the recruits were infected during the period between pre- and post-vaccination bleeding.

B/Ann Arbor/86

Response to this component again was excellent. Individuals with titers of <8 fell from 47% to 1% and the percent with titers >32 before vaccination rose from 19% to 88%. This rise in the antibody levels is far greater than we have observed in the last three or four years with Influenza B vaccine and may well reflect the fact that Influenza B was widely prevalent last year and individuals were well primed for vaccine response.

ANTIBODY RESPONSE IN PERMANENT PARTY (Table 7)

H3N2

A/Mississippi/85

Titers against the A/Mississippi/85 strain were remarkably high in the prevaccination sera. All had pre-vaccination titers of ≥8; 83% had titers ≥32. After vaccination the percent with titers of ≥32 had risen to 98%.

A/Leningrad/86

Prevaccination titers were higher in the permanent party than in the recruits but their response to the vaccine was not nearly as good. Before vaccination 12% had titers <8 and 38% had titers ≥32. After vaccination 2% had titers <8 and 62% had titers ≥32.

A/Chile/83

Again the prevaccination titers were high in this population with 1% having titers <8 and 89% having titers ≥32. In the post-vaccination sera only 1% had titers <8 and 96% had titers ≥32.

A/Taiwan/86

Thirty-five percent had titers <8 before vaccination and 24% after vaccination. The percent with titers ≥32 were respectively 24% and 32%. These individuals were vaccinated approximately one month before the recruits. The fact that there was little change in titer suggests that they were not affected by the outbreak of influenza. The post-vaccination sera were collected 15 November.

B/Ann Arbor/86

Prevaccination titers showed that 19% had titers <8 in the prevaccination sera and 7% in the post-vaccination sera. After vaccination the percent of individuals with titers ≥32 had risen from 41% to 58%. This response is considerably less than that observed in the recruits.

ANTIBODY RESPONSE IN RETIREMENT HOME RESIDENTS (Table 8)

H3N2

A/Mississippi/85

Five percent of individuals had titers <8 before vaccination and 1% after vaccination. Titers of ≥32 were found in 60% before vaccination and 88% after vaccination.

A/Leningrad/86

Twenty-two percent had titers <8 before vaccination and 8% after vaccination. Titers ≥32 were found in 30% before vaccination and 60% after vaccination.

H1N1

A/Chile/83

In prevaccination sera 13% of individuals had titers <8 and 41% had titers ≥32. After vaccination 3% had titers <8 and 64% had titers ≥32.

A/Taiwan/86

Forty-four percent had titers <8 before vaccination and only 18% had titers ≥32. After vaccination 31% still had titers <8 and only 24% had titers ≥32.

These individuals were vaccinated on 15 October and had their post-vaccination bloods collected on 17 November. Like the permanent party, they probably were not hit by the outbreak of Influenza H1N1 which apparently hit recruits during the latter part of November.

B/Ann Arbor/86

Twenty-nine percent of individuals had titers <8 before vaccination and 31% had titers ≥32. Following vaccination 8% had titers <8 and 53% had titers ≥32. These results are slightly lower than those observed in the permanent party, who are vaccinated annually. Vaccinated individuals usually show relatively poor response to a second injection of aqueous vaccine. Many of these retirement home residents had been vaccinated previously. Almost all are over 55 and large numbers are considerably older than that.

The results of vaccination are shown in a different form in Table 9, which shows the percentages having increase in antibody titer following vaccination of 0, 2-fold, 4-fold or more. With this form of presentation, the superior response of the recruits is emphasized and the difference between the permanent party and retirement home individuals is again brought out. The striking response of the recruits to the H1N1 strains is in marked contrast to the permanent party and retirement home residents, and again suggests that many of the antibody increases were due to infection during the period between the two vaccination bleedings.

OCCURRENCE OF INFLUENZA

Influenza A H1N1 was first detected at Lowry Air Force Base during the week beginning November 10. Substantial numbers of cases began to occur early in December and peaked just before the Christmas break. It was obvious from the start that the students were faring better than the permanent party. In the student population there was no sharp epidemic peak, rather a small number of cases, between 1 and 5 at the most, occurring each week over the 12-week period between November 10 and February 9 (Figure 1, Table 10). What would have happened had the students remained on the Base during the Christmas break rather than scattering across the country is obviously not known. Monovalent Taiwan vaccine had been given to a small number of students at Lackland Air Base during December and after the first of January all recruits received both standard and Taiwan vaccine. At Lowry Air Force Base a number of students received a supplemental dose of monovalent vaccine during early January. The exact numbers and dates of vaccine administration were not obtainable.

There are two artifacts in Table 10 which should be noted. First, the week of November 24th shows a sharp drop in the number of febrile URIs. That was the week of Thanksgiving when most students and many permanent party were not on the Base. Second, the weeks of December 22-29 were the Christmas holidays when virtually all students were gone. A large number of permanent party, however, remained in the area.

The number of individuals coming to the Clinic with URI symptoms and temperatures $\leq 99^{\circ}F$ is shown in the left hand column (Table 10). These numbers include both students and permanent party. It is of interest to note the very sizable increase in the number of patients who reported without fever at the time of the influenza peak. The peak number of 225 coincides with the peak of the influenza epidemic when 43 patients were diagnosed as having had influenza. It is probable that many of these patients had mild influenza.

Then, in contrast to the students, the permanent party began to have cases the same week, but the number of cases rose quite sharply. During the week of December 8, influenza became the dominant illness and a very sharp peak followed during the next week (Figure 2). Many of the permanent party remained in Denver over the Christmas holiday. All of the 8 individuals seen during the two weeks of the Christmas break had confirmed influenza. There was then a gradual falloff, with the last case occurring the week of February 9.

The determination of the exact number of cases in the permanent party was complicated by the fact that during the Christmas break many of the individuals who became ill went to Fitzsimons Army Hospital rather than to the Lowry Clinic. We were able to obtain the number by weeks and the oral temperatures of the URI patients who were seen. We accordingly estimated the additional number of individuals who probably had influenza by assuming that the ratio of the number of cases of influenza/febrile URIs would be the same at Fitzsimons as at Lowry Air Force Base. This added 23 more cases to the permanent party and 8 to the students. This assumption was supported by the fact that the distribution of temperatures of URI patients was virtually identical to that of those who were seen at Lowry Air Force Base during the period when influenza was prevalent. The temperatures of more than 35% of influenza patients was over 101°. During the later period when no influenza was occurring, this figure was far lower.

Further analysis of the attack rates in different units shows that the higher rate in the permanent party was due in large measure to the fact that this group included temporary duty Air Force personnel and personnel from other services. Twelve of 27 cases of influenza in these categories occurred in persons who had not been vaccinated in 1986. The highest rates were seen in the temporary duty personnel and in the personnel from other services, including FTOs. In Air Force TDY, there were 18 cases in 605 individuals (3.0%) and in the other services, 9 cases among 232 individuals (3.9%). There is no way of getting an accurate denominator on the proportion of individuals vaccinated in these two groups.

The only group in which an estimate of vaccine efficacy could be made was in the regular Air Force personnel stationed at Lowry Air Force Base. In this group, in which vaccination coverage was reported to be 94%, there were 51 cases, 46 in vaccinated and 5 in unvaccinated persons. This gives an attack rate of 1.2% in the vaccinated and a rate of 2.0% in the unvaccinated, a protective efficacy of 40%. These are very small numbers and the data are difficult to interpret because there is so much variability in what is classified as an unvaccinated person. Some of these were individuals who had been vaccinated in 1985, others not for the past five or six years. The only conclusion that can be drawn is that the rate in the vaccinated permanent party drops down to a level comparable to that in the students, and that the annual revaccination is probably doing some good.

Evaluation of vaccine effectiveness in students was impossible because there were no unvaccinated Air Force students identified throughout the winter. The attack rate was estimated to be 1.2%.

RELATIONSHIP BETWEEN HI ANTIBODY TITER AND ATTACK RATE

Very soon after the development of the HI test for the diagnosis of influenza, it was noted that the cases of influenza tended to be concentrated in individuals with titers of <8 or 8. It was also shown that HI titers in general paralleled neutralizing antibody titers. It was essential that (1) the test be run with a virus isolated from the epidemic or one very closely related to it; (2) a whole virus was needed in the test rather than ether split virus; and (3) inhibitors were removed from the sera under test. This laboratory has shown repeatedly that for the Influenza A strains of the H3N2 subtype, the so-called protective titer was 32. This was confirmed again in the winter of 1984-85. In the winter of 1985-86 a relatively large number of cases at Lowry Air Force Base permitted a determination that with Influenza B also a titer of 32 was protective. Data with Influenza A of the H1N1 subtype have been less completely studied and it was therefore considered important to use data from this year's relatively large number of confirmed cases of Influenza A H1N1 to determine the protective titer for this subtype of Influenza A.

Acute phase sera were available from 58 permanent party with confirmed influenza who had received vaccine, and from an additional 16 persons who had not been vaccinated. There were 18 students with confirmed influenza from whom acute phase sera were available. The distribution of post-vaccination HI antibody titers was determined in 75 permanent party and 75 students. It was assumed that there would be relatively little drop in antibody titer during the two or three months before the epidemic hit, and as a result the distribution of antibody titers would be essentially the same when the epidemic arrived. The number of individuals in the student group was approximately 2,500, and in the Air Force permanent party 4,100.

In students the number of cases was small, but there was a concentration of cases in the <8 to 16 range, with 17 of 1,375 students appearing with illness (an attack rate of 1.2%). In contrast, only a single patient was detected among the 1,125 patients with titers of $\geq$32. Even with these small numbers, this is a significant difference.

In the permanent party it appeared that the highest attack rate (6%) occurred in individuals with titers of <8. With increasing titer, the attack rates fell progressively up to 32, but the occurrence of three cases in persons with titers of 32 and three in individuals with titers of $\geq$64 failed to provide the clean cutoff observed in H3N2 Influenza A and Influenza B. Nonetheless, the difference in three individuals with titers of <8 to 16 and those with titers $\geq$32 was significant (Table 11).

Among the 16 individuals who had not been vaccinated in 1986, the concentration of patients with very low titers was even more striking. Fourteen of 16 individuals (88%) had titers of <8 or 8 and only two of 16 had titers of $\geq$32.

It has been observed previously during almost all H1N1 outbreaks that the H1N1 subtype does not produce the sharp falloff of attack rate observed in the other types of influenza virus. The high titers observed in a few individuals presumably do not represent neutralizing antibody. In 1957 in a similar situation we tested a number of individuals with high HI titers with mouse neutralization tests and found little or no neutralizing antibody.

With Influenza B and Influenza A H3N2 the attack rates in individuals at or above the "protective" antibody level are usually from 10 to 20-fold lower than those observed in individuals with titers <8. This relationship appeared to hold for H1N1 A/Taiwan/86 in the student population, but in the permanent party the difference between these two was considerably smaller. When simple and reasonably inexpensive neutralization tests become available, it will be important to test those individuals who acquire clinical influenza in the face of high HI antibody titers in order to determine what their neutralizing antibody titers actually are.

AGE DISTRIBUTION OF CASES OF INFLUENZA

When the Russian strains of H1N1 Influenza A appeared in 1977, attack rates in young individuals were extremely high; it was very uncommon to find a case in anyone over 23 years of age. This was interpreted to mean that individuals who had been alive through the late 1940s and 50s and had their first experience with Influenza A with an H1N1 virus had developed for the most part a lasting immunity. It was for this reason interesting to observe 10 years later that there was a similar age cutoff but at a considerably higher level, namely around 35. The distribution by age of the permanent party Air Force personnel at Lowry was obtained through the assistance of Col. Hutchison. The age distribution in 68 confirmed cases of influenza in the permanent party is shown in Table 12. In the age group from 18 to 25, i.e., in individuals born between 1961 and 1968, and in persons between 26 and 30 the attack rates were respectively 2.1% and 2.6%. In those between 31 and 35, born between 1951 and 1955, the rate dropped off to 1%, and in those between 36 and 40, the rate was again halved to 0.5%. Among the relatively small number of individuals over 41 years of age, no cases were observed.

In contrast, the age distribution of individuals in the same population who came in with febrile URIs but did not have influenza was different (Table 13). In this situation the highest attack rate was in the 18-25-year-old group, next in the 25-30 group and thereafter the rates did not show the consistent dropoff noted in patients with influenza. There were four illnesses in individuals over 41 years of age.

This distribution was considered surprising in 1977 but it has been observed in all subsequent H1N1 Influenza outbreaks. It appears that protection in this older segment of the population is not due solely to humoral antibodies since a substantial proportion of these individuals had HI titer ≤ 8. The fact that their first experience with Influenza A virus was an H1N1 presumably provided the original antigenic stimulus which has been boosted by subsequent infection to maintain a lasting immunity against other H1N1 viruses. Other factors which play a part in resistance to influenza illness remain poorly defined.

During the past winter we had under observation some 2,000 elderly individuals in 21 nursing homes. These institutions, which had been hit hard in the previous seasons by Influenza A H3N2 and Influenza B, had virtually no influenza during this past winter. Lt. Col. Martin Evans made a similar observation at Lackland Air Force Base in the Air Force retirement home where Influenza A/H1N1 had virtually no impact.

INAPPARENT INFECTION

We have noted in the past that even when the rates of febrile influenza were relatively low, there was evidence that the virus spread widely in the student population where it presumably caused inapparent infections. It was shown in Table 10 that clinic visits for URI without fever increased sharply during periods when influenza was occurring at the highest rates. For example, in the week of December 15, the number of URIs without fever rose to 225, and one must assume that the large part of the excess over the background rate of respiratory infection was composed largely of individuals who had mild clinical influenza. This excess probably exceeded the number of febrile URIs during that week.

In order to determine whether there were additional infections in the student population, we utilized the HI titers for A/Taiwan/86 in the acute phase serum of patients who came in with febrile URIs but did not have influenza. We compared the titers of 25 individuals who had become ill before influenza became prevalent on the Base, that is, between 2 November and 10 December, with those of individuals who came in between 12 February and 7 May. All had received only the standard vaccine. In the former group, 28% of the individuals had titers of <8; in the latter group, only 4% had titers of <8. At the other end of the scale, 32% in the second group had titers $\geq$128 compared to 12% in the group bled before the epidemic. This suggests that 20% of the student population were infected during the intervening period. The figure is comparable to those seen in numerous previous outbreaks. The data also indicate that their immune status had been greatly improved at a price of very little morbidity.

When the data from the permanent party were analyzed in the same way, no difference was found in the distribution of titers between those bled before and after the epidemic, suggesting that the virus did not infect as many persons in the permanent party as among the students.

COMPARISON OF DIFFERENT TESTS FOR THE DIAGNOSIS OF INFLUENZA

There were 15 students and 77 permanent party from whom we obtained throat washings for virus information and paired sera for HI and CF tests. By far the most useful diagnostic test during this H1N1 outbreak was the HI test using the homologous virus A/Taiwan/86 (86%). Virus isolation was relatively insensitive, being positive in only 66% of cases. CF tests, which worked extremely well during the Influenza B epidemic last year, were considered less effective with a positive result in only 61% of individuals.

The relatively low rate of recovery of virus from throat washings from patients with confirmed H1N1 influenza is similar to our experience in other outbreaks of H1N1 influenza. This rate is considerably lower than that observed with H3N2 viruses, where recovery rates in RMK tissue culture may run as high as 90%, or Influenza B, where the recovery rate is usually in the range of 70–75%. The recovery rate in chick embryos was considerably lower; however, few strains were tested. All remained non-avid during the early passages.

Complement fixation tests for diagnosis of Influenza A have consistently been less useful than for Influenza B. The allantoic fluid antigens which were used test mainly for common Influenza A antigens and do not discriminate between Influenza A H3N2 or H1N1. The vaccine contains twice as much Influenza A as it does Influenza B antigen, and titers tend to be higher after vaccination for Influenza A than for Influenza B. As a result, four-fold or greater increases in titer are less likely to be seen in vaccinated patients with Influenza A than with Influenza B.

OTHER RESPIRATORY DISEASES

Adenovirus Infections

Since oral adenovirus vaccine began to be administered at Lackland Air Force Base, there has been almost no evidence of illness caused by these viruses at Lowry Air Force Base. This year only three adenovirus infections were confirmed by complement fixation tests.

Chlamydia TWAR

Thomas Grayston and others have recently reported that a previously unidentified member of the chlamydia family, TWAR, not psittacosis virus, has caused outbreaks of febrile URI in military populations as well as in elderly people in whom upper respiratory infection is frequently complicated by pneumonia. It was his impression that, if we screened patients with psittacosis antigen, we would pick up a number of cases if the disease were prevalent. Accordingly, we obtained psittacosis antigen through the assistance of Col. Bancroft at Walter Reed Army Institute for Research and tested slightly over 257 pairs during the period from January to May 1986. One patient showed an antibody rise from <8 to 256. Four patients had titers of 16 in both acute and convalescent sera and 14 patients had titers of 8; the remainder were <8. It appeared that, at least during this season, chlamydia TWAR was not an important cause of illness in Air Force personnel stationed at Lowry Air Force Base.

Group A Streptococcal Infection

There was a report this year from Utah that acute rheumatic fever had again become active in Utah, and because of Lowry's past bad experience with A.R.F., it seemed wise to look into the situation there. Mr. James, formerly a Master Sergeant, had been stationed at Lowry in the Microbiology Laboratory since the 1950s. He was familiar with streptococcal technique and noticed early in the spring a number of the strains produced mucoid colonies resembling those seen in Utah. He sent seven strains to Dr. Kaplan at the University of Minnesota, who runs the WHO streptococcal laboratory there. All were type M-18. At about that time a single case of acute rheumatic fever was diagnosed at Fitzsimons in a member of the Lowry student population.

There was considerable ignorance about what needed to be done because none of the personnel at Lowry were old enough to have been aware of the fact that ARF had been a serious problem at the Base in the 1940s and 1950s. Fortunately, the situation seemed to take care of itself without any particular action. The number of positive throat cultures obtained each week are presented in Table 10. Streptococcal infections occur throughout the year, but never at a high level. In only one week did the number of cases exceed four. During the spring when the mucoid colonies were recognized, the number of cases per week showed no sharp increase. If streptococcal disease again becomes a serious problem, it may be necessary to go back to the procedures which were effective in the 1950s and to educate the medical staff on what needs to be done.

PERSPECTIVE

This program began in 1952 with the main goals of determining the causes of febrile respiratory disease inthe Air Force student population at Lowry Air Force Base and of devising means of preventing them. There has been substantial progress. Adenovirus disease, which in the 1950s and 1960s was the major cause of morbidity, has been virtually eliminated since oral vaccines have been administered to all recruits from the time of arrival at Lackland Air Force Base. The second major cause of concern, namely streptococal pharyngitis, which might cause rheumatic fever, also has not been a serious problem. However, it now appears that rheumatic fever may again be appearing in the Rocky Mountain area. We have looked over the years for other causes of febrile respiratory illness by testing for enteroviruses, coronaviruses, respiratory syncitial virus, parainfluenza viruses and, most recently, chlamydia TWAR. We have found small numbers of cases due to each of these agents, but none appeared to cause major morbidity.

Influenza remains a potential problem. Before vaccination was universal in the Armed Services, almost every time influenza appeared in the community, there was a sharp outbreak in the student population at Lowry Air Force Base. On two occasions when the population was unvaccinated, there were major epidemics, first in 1957 when Asian influenza A (H2N2) appeared, the second in 1977 when the Russian strain of H1N1 appeared. In both instances, attack rates were so high that training operations were seriously disrupted.

Early in this program a number of studies were done which clearly demonstrated that inactivated vaccine could greatly reduce the incidence of clinical illness caused by influenza viruses. Since the early 1970s it has been considered immoral to conduct controlled studies of influenza vaccines. It is held that, with vaccine efficacy established, it is not right to withhold vaccine from anyone. Hence, the only method of assessing vaccine effectiveness has been to determine the amount of illness and to relate it to the antibody status of the group under study. These students have done very well over this period with the exception of the two years noted. The attack rates have not exceeded more than 1% or 2% in recent years. The program at Lackland Air Force Base has been tightened up to the point where it is extremely rare to find an unvaccinated student coming into Lowry Air Force Base. Response to all three components of the vaccine has usually been brisk and vaccine reactions have become unimportant with recent preparations. There is also evidence when influenza does appear, there is not a sharp outbreak but a lingering low-grade affair lasting anywhere from 8 to 15 weeks, during which a large proportion of the population appears to have been infected and presumably acquired immunity without significant morbidity.

In the permanent party the situation is slightly different. Annual revaccination evokes far less antibody response than is observed in recruits and attack rates in vaccinated personnel of clinical influenza have always been slightly higher than in the students. Attack rates of Influenza A H3N2 and Influenza B tended to be higher in older segments of the permanent party whereas Influenza A H1N1 has been restricted to those in the younger segments. Vaccination coverage of permanent party at Lowry has reached now well over 90%.

Antigenic drift has continued to occur and to date it has had little effect on the usefulness of H3N2 vaccine. However, last year Influenza B showed significant antigenic drift and caused more illness than we have observed previously. During the 1986-87 season H1N1 influenza showed antigenic drift and there was again a slight increase in the number of observed illnesses. The rates did not at any time exceed 2% in the Air Force personnel.

Collaboration has been established with the staff at Lackland Air Force Base for the past five years. Paired sera have been obtained from students and permanent party at vaccination. These have been most valuable in assessing the adequacy of the three components in the vaccine and also in testing for antibody in these new strains which show significant antigenic drift. These data are essential in deciding whether or not there is need to change the antigenic components of the vaccine.

The question now is, Where should we go from here? Should we be content to believe that we have reached the point where influenza is no longer a significant problem or should we recognize that all three types of influenza continue to show antigenic drift and that one of these days we undoubtedly will have a pandemic of Influenza A due to some antigenic shift?

Students respond very well to each of the three components of the current vaccine. In the permanent party, however, the response has been less satisfactory and additional doses of aqueous vaccine evoke no additional response. Other approaches should be considered.

We know from earlier experience that adjuvant vaccines of the Salk type produced a greatly enhanced antibody response in individuals even if persons have substantial antibody levels prior to vaccination. These antibody levels remained high enough to be protective for a period of several years. If it was possible to find an acceptable adjuvant vaccine, it might be possible to eliminate annual revaccination and develop a program of revaccination only when there had been very significant antigenic drift.

Consideration should also be given to the use of live vaccines which might produce a more lasting immunity. The most convincing evidence of the usefulness of live vaccines has been provided by studies in individuals who were seronegative. In the permanent party, one the other hand, most individuals have antibody and, until the efficacy of live vaccines has been demonstrated in individuals of this sort, it would be premature to suggest their use in Air Force personnel. A great deal of work needs to be done before live vaccine is substituted for inactivated vaccine. The question of whether or not amantadine or rimantadine should be used prophylactically is frequently raised but the use of a drug of this type in the uniformly vaccinated military personnel does not appear desirable at present. The cost would be increased and drug reactions would be expected.

In past years Influenza A H3N2 vaccine has protected extremely well. In 1985-86, Influenza B and in 1986-87, Influenza A H1N1 caused a moderate amount of illness because of significant antigenic drift. We still need more data on the influenza virus and on immunity to influenza. The present

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Figure 1

Febrile Upper Respiratory Infections (URI) at Lowry AFB. 1986-1987

Students

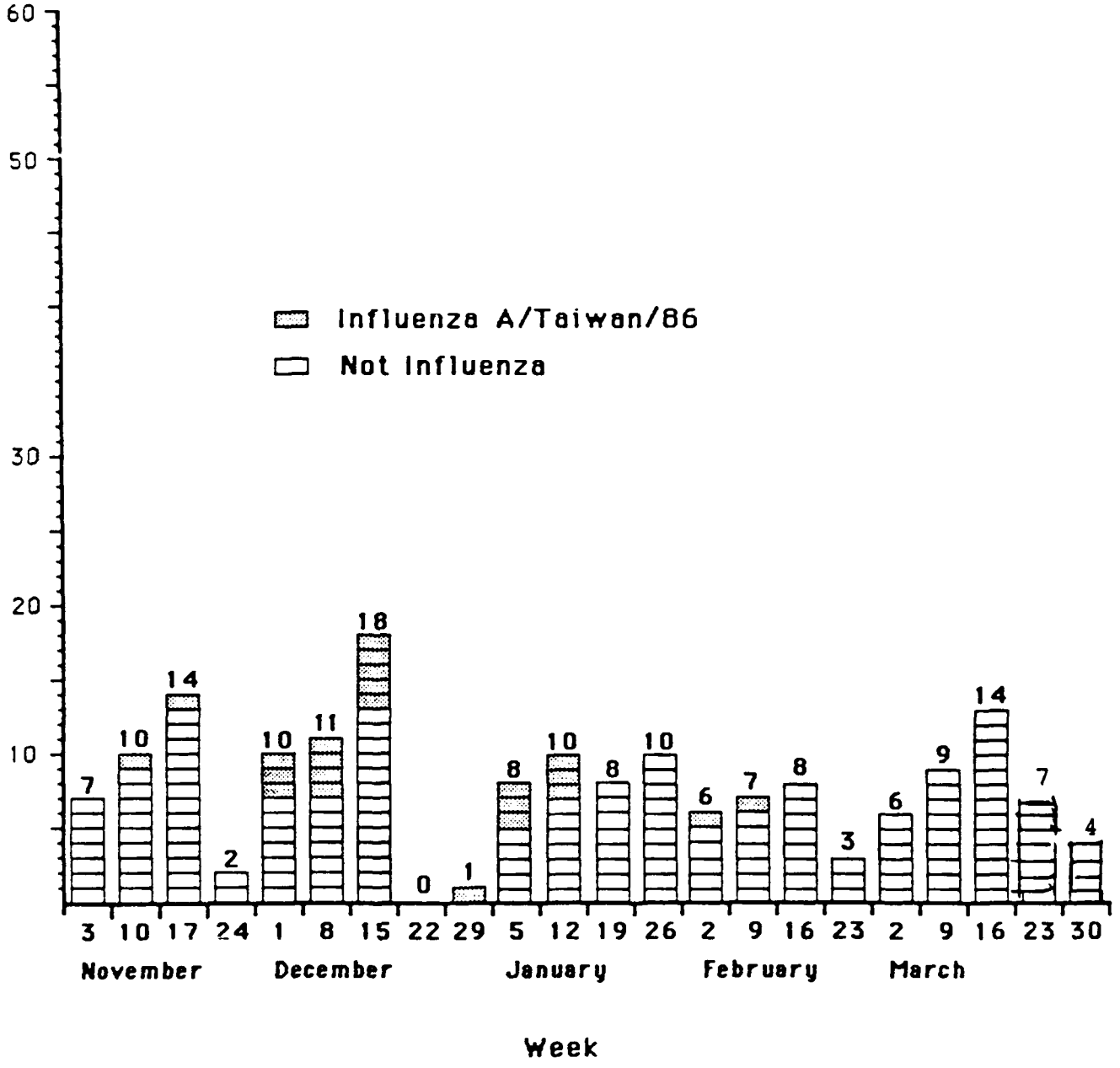

Figure 2

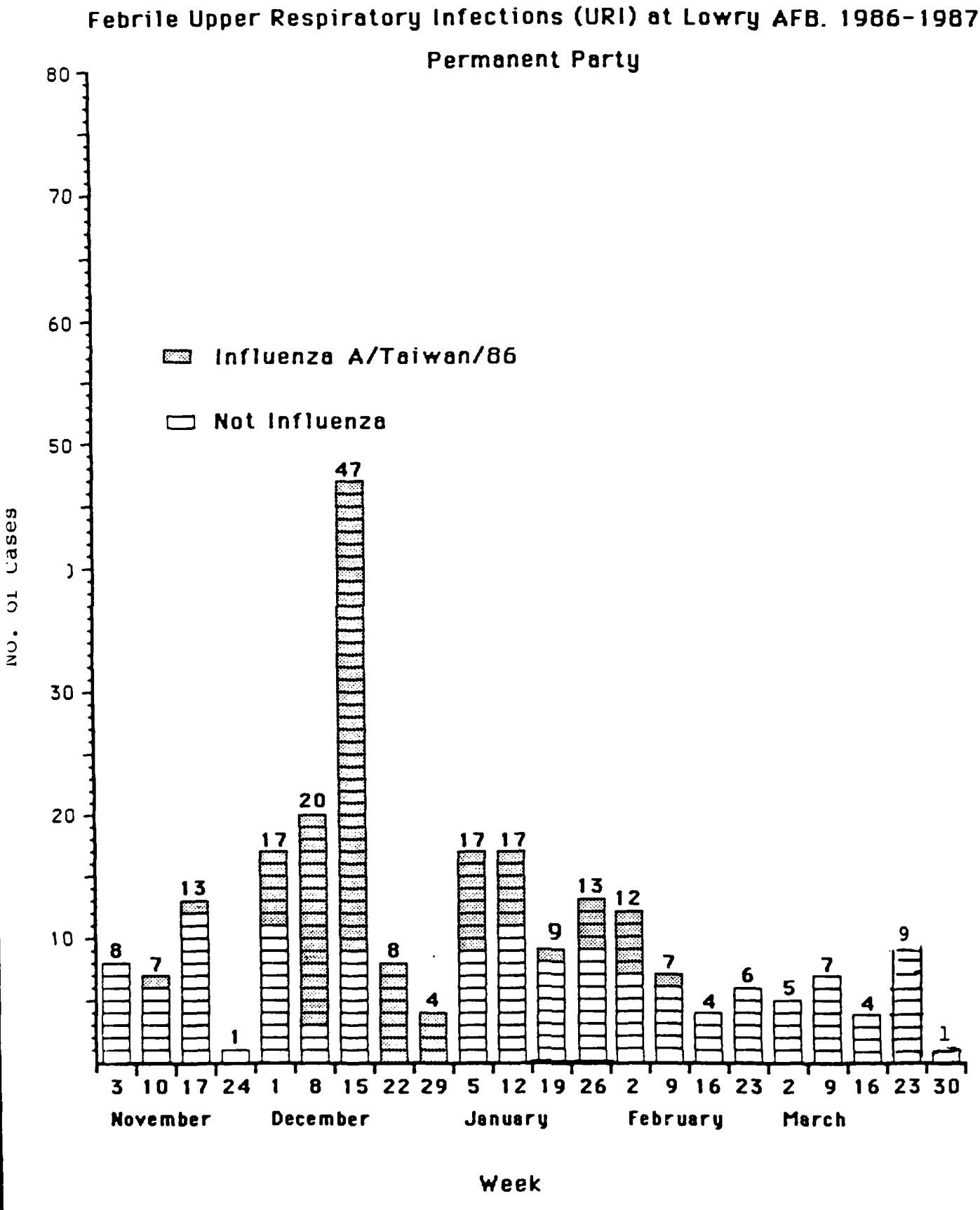
Febrile Upper Respiratory Infections (URI) at Lowry AFB. 1986-1987
Permanent Party
Influenza A/Taiwan/86
Not Influenza
NO. OF CASES
80
70
60
50
40
30
20
10
8
7
13
1
17
20
47
8
4
17
17
9
13
12
7
4
6
5
7
4
9
1
3 10 17 24 1 8 15 22 29 5 12 19 26 2 9 16 23 2 9 16 23 30
November
December
January
February
March
Week

Table 1

H.I. antibody titer of acute and convalescent sera of 23 students and 26 permanent party who had influenza B in tests with B/Denver/2/86 and B/Ann Arbor/1/86.

Group	Antigen	Serum	Cumulative % with H.I. titer of: <8	8	16	32	64	128	256	512	1024	% with 4X rise
Student #23	B/Denver/2/86	Acute	74	26	17	4	4	-	-	-	-	
			78	22	13	4	4	-	-	-	-	
		Conv.	17	83	69	52	35	18	13	8	4	65
	B/Ann Arbor/ 1/86	Acute	70	30	21	4	4	-	-	-	-	
		Conv.	4	95	78	61	39	26	13	9	9	70
Permanent Party #26	B/Denver/2/86	Acute	62	38	19	-	-	-	-	-	-	
		Conv.	15	85	81	58	39	12	8	4	-	78
	B/Ann Arbor/ 1/86	Acute	50	50	27	-	-	-	-	-	-	
		Conv.	4	96	92	73	35	20	12	4	-	83

Table 2

Comparison of estimated influenza attack rates at different H.I. antibody levels in tests with B/USSR/83 (vaccine strain) ether split and epidemic strain B/Denver/2/86.

Group	Antigen	Titer	Est. no. of persons	No. of Cases	Attack Rate(%)
Student	B/Denver/2/86	<8-16	2448	46	1.9
		≥32	952	2	0.2
		≥64	0	0	0
		≥128	0	0	0
		Total	3400	48	1.4
	B/USSR-E.T.	<8-16	136	16	11.7
		≥32	3264	32	1.0
		≥64	2856	2	0.07
		≥128	2448	4	0.2
		Total	3400	48	1.4
Permanent Party	B/Denver/2/86	<8-16	5336	68	1.3
		≥32	464	0	0
		≥64	232	0	0
		≥128	0	0	0
		Total	5800	68	1.2
	B/USSR-E.T.	<8-16	1160	30	2.6
		≥32	4640	38	0.8
		≥64	3248	20	0.6
		≥128	1624	10	0.6
		Total	5800	68	1.2

Table 3

Comparison of pre-and post-vaccination HI antibody titers of 25 permanent party and post-vaccination titers of 25 students in tests with B/USSR/83, B/Ann Arbor/86, and B/Den/2/86.

Antigen	Group	Serum	Cumulative Percent with HI Antibody Titer of									% Fold-rise	
			< 8	8	16	32	64	128	256	512	1024	2X	4X
B/USSR/83	PP	Pre	16	84	80	60	32	-	-	-	-		
E.T.		Post	4	96	84	80	56	28	-	-	-	64	8
	Student	Post	-	100	100	96	84	72	48	40	32		
B/AA/86	PP	Pre	64	56	32	8	-	-	-	-	-		
W.V.		Post	36	64	44	8	-	-	-	-	-	16	4
	Student	Post	40	60	36	32	20	8	4	4	4		
B/Den/2/86	PP	Pre	48	52	20	4	-	-	-	-	-		
W.V.		Post	40	60	32	8	4	-	-	-	-	20	4
	Student	Post	52	48	36	28	24	8	4	4	4		

Table 4

H.I. antibody titers of pre- and post-vaccination sera of 25 permanent party and post-vaccination titers of 24 students in tests with influenza A (H1N1) strains A/Chile/83 and A/Taiwan/86.

Group	Antigen	Serum	Cumulative % with titer of 8	8	16	32	64	128	256	512	1024	% Fold-rise 2X	4X
Perm. Party #25	A/Chile/83	Pre	4	96	84	52	16	-	-	-	-		
		Post	-	100	92	72	40	8	8	-	-	44	8
Student #24		Post	-	100	100	96	88	71	46	28	25		
Perm. Party #25	A/Taiwan/86	Pre	36	64	48	32	12	-	-	-	-		
		Post	28	72	52	44	28	4	4	-	-	24	4
Student #24		Post	20	80	49	37	29	16	8	8	-		

Table 5

Comparison of H.I. antibody titers for A/Taiwan/86, and A/Chile/83 of students before and after receiving standard trivalent vaccine and after monovalent A/Taiwan vaccine booster given 2-3 months after standard vaccine.

Test Antigen	Serum Specimen	Cumulative percent with H.I. titers >								
		<8	8	16	32	64	128	256	512	1024
A/Taiwan/86	Pre-Trivalent (40)	92	8	-	-	-	-	-	-	-
	Post-Trivalent 2-3 mo. (34)	28	72	62	45	37	32	12	10	8
	Post-Monovalent 3 wks. (34)	-	100	100	100	95	92	71	53	41
A/Chile/83	Pre-Trivalent (40)	23	77	41	24	11	3	-	-	-
	Post-Trivalent 2-3 mo. (34)	-	100	100	100	100	97	94	82	62
	Post-Monovalent 3 wks. (34)	-	100	100	100	100	100	97	94	76

Table 6

Results of HI tests with serum pairs from 75 recruits at Lackland Air Force Base who received vaccine immediately on arrival at the Base. The A/Leningrad virus was tested against only 50 recruits. Bled 11/4 and 12/2/86.

Test Antigen	Serum	% <8	Cumulative %> 8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	27	74	57	44	25	18	11	4	0
	Post	0	100	99	99	96	91	84	80	65
A/Leningrad/86 (X91)	Pre	30	70	34	18	8	0	0	0	0
	Post	4	96	94	86	78	70	60	34	20
A/Chile/83* (H1N1)	Pre	24	76	49	30	11	5	1	0	0
	Post	1	100	100	100	99	98	94	87	79
A/Taiwan/86 (H1N1)	Pre	81	18	2	1	0	0	0	0	0
	Post	4	96	92	79	68	51	32	17	8
B/Ann Arbor/86*	Pre	47	52	28	19	6	5	0	0	0
	Post	1	99	95	88	68	37	28	9	5

*Strain contained in the vaccine.

Table 7

Results of HI tests with serum pairs from 75 permanent party at Lackland Air Force Base who received vaccine. The A/Leningrad virus was tested against serum from only 50 permanent party. Bled 10/6 and 11/5/86.

Test Antigen	Serum	% <8	Cumulative % > 8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	0	101	94	83	64	47	54	33	12
	Post		99	99	98	90	65	49	24	13
A/Leningrad/86 (X91)	Pre	12	88	58	38	20	12	6	2	0
	Post	2	98	84	62	40	20	8	2	0
A/Chile/83* (H1N1)	Pre	1	99	96	89	73	48	33	25	16
	Post	1	99	99	96	89	64	44	29	13
A/Taiwan/86 (H1N1)	Pre	35	65	41	24	16	8	1	1	0
	Post	24	76	48	32	17	9	2	1	1
B/Ann Arbor/86*	Pre	19	81	57	41	24	8	7	3	0
	Post	7	93	82	58	38	17	9	4	1

*Strain contained in the vaccine.

Table 8

Results of HI tests of paired sera from 75 residents of the Air Force Retirement Home at Lackland Air Force Base in San Antonio. All received standard vaccine. The A/Leningrad virus was tested against serum from only 50 residents. Bled 10/15 and 11/17/86.

Test Antigen	Serum	%	Cumulative % >							
		<8	8	16	32	64	128	256	512	1024
A/Miss/85* (H3N2)	Pre	5	94	79	60	47	30	13	4	1
	Post	1	100	96	88	81	58	44	23	11
A/Leningrad/86 (X91)	Pre	22	78	50	30	16	6	2	0	0
	Post	8	92	80	60	34	22	14	6	2
A/Chile/83* (H1N1)	Pre	13	86	66	41	22	11	6	1	0
	Post	3	98	89	64	44	21	10	3	0
A/Taiwan/86 (H1N1)	Pre	44	55	26	18	10	3	3	2	1
	Post	31	70	35	24	12	5	4	1	0
B/Ann Arbor/86*	Pre	29	70	51	31	18	5	1	1	0
	Post	8	92	73	53	41	12	5	1	0

*Strain contained in the vaccine.

Table 9

Comparison of fold increase in antibody titer in HI tests with five virus antigens following vaccination in recruits, permanent party and residents of Air Force Retirement Home. All individuals received standard vaccine containing 15 mcg each of A/Mississippi/85, A/Chile/83 and B/Ann Arbor/86.

Strain	Group	Percent with HI Titer Rise of 0	2-fold	≥4-fold
A/Miss/85				
	Recruits	3	7	91
	Permanent Party	39	29	23
	Retirement Center	29	32	39
A/Leningrad/86				
	Recruits	6	4	90
	Permanent Party	42	36	22
	Retirement Center	36	36	28
A/Chile/83				
	Recruits	1	4	95
	Permanent Party	52	39	9
	Retirement Center	51	37	23
A/Taiwan/86				
	Recruits	4	8	88
	Permanent Party	65	28	7
	Retirement Center	77	19	4
B/Ann/Arbor/86				
	Recruits	8	16	76
	Permanent Party	37	47	16
	Retirement Center	47	29	24

Table 10

Number of Upper Respiratory Infections (URI) at Lowry AFB, 1986-87

Week	URI w/o Temp.	Febrile URI*			Influenza A			Strep Phar.
		Total	S.	P.P.	Total	S.	P.P.	
3 Nov.	122	15	7	8	-	-	-	1
10	112	17	10	7	1	1	-	1
17	192	27	14	13	2	1	1	1
24	123	5	4	1	-	-	-	
1 Dec.	154	25	8	17	8	3	5	2
8	184	31	11	20	21	4	17	1
15	225	65	18	47	43	5	38	1
22	47	8	0	8	8	-	8	1
29	75	5	1	4	5	1	4	1
5 Jan.	160	25	8	17	11	3	8	2
12	148	27	10	17	9	3	6	3
19	123	17	8	9	1	-	1	4
26	161	23	10	13	4	-	4	2
2 Feb.	149	18	6	12	6	1	5	2
9	159	14	7	7	2	1	1	1
16	129	12	8	4	-	-	-	9
23	135	9	3	6	-	-	-	2
2 Mar.	149	11	6	5	-	-	-	3
9	132	16	9	7	-	-	-	4
16	158	18	14	4	-	-	-	1
23	131	16	7	9	-	-	-	4
30	106	5	4	1	-	-	-	3

*Temp $\geq 99^{o}$F

(Continued on next page)

Table 10 (Continued)

Week	URI w/o Temp.	Febrile URI*			Influenza A			Strep Phar.
		Total	S.	P.P.	Total	S.	P.P.	
6 Apr.	132	2	1	1	-	-	-	3
13	132	12	19	2	-	-	-	4
20	123	9	5	4	-	-	-	-
27	138	13	6	7	-	-	-	3
4 May	104	10	7	3	-	-	-	2
11	120	12	8	4	-	-	-	3
Total	3825	467	210	257	121	23	98	63

*Temp $\geq 99^{0}F$

Table 11

Relationship between acute serum H.I. antibody titer for A/Taiwan/86 and attack rate in permanent party and students who had been vaccinated in 1986 with trivalent vaccine containing A/Chile/83.

Population	Titer	Est. % of Persons	Est. # of Persons	No. of Cases	Attack Rate(%)		
Permanent Party	<8	10	410	27	6.6		
	8	35	1435	18	1.0	51/2665	1.9
	16	20	820	6	0.7		
	32	25	1025	4	0.4	7/1435	0.5
	≥64	10	410	3	0.7		
		Total	4100	58	1.4		
Students	<8	28	700	8			
	8	10	250	2	1.1	17/1375	1.2
	16	17	425	7	1.6		
	32	7	175	1	0.6	1/1125	0.09
	≥64	38	950	0	0.0		
	Total	100	2500	18	0.7		

Table 12

Age distribution of 68 Air Force permanent party patients with confirmed A/Taiwan/86 influenza

Age	Year of Birth	No. of Persons	No. of Cases	Rate (%)
18-25	1961-68	1179	25	2.1
26-30	1956-60	1215	32	2.6
31-35	1951-55	809	8	1.0
36-40	1946-50	570	3	0.5
>41	Before 1945	353	0	0.0
	Total	4126	68	1.6

Table 13

Age distribution of 114 Air Force permanent party febrile URI patients who did not have influenza

Age	Year of Birth	No. of Persons	No. of Cases	Rate (%)
18-25	1961-68	1179	55	4.7
26-30	1956-60	1215	26	2.6
31-35	1951-55	809	16	1.6
36-40	1946-50	570	11	1.9
>41	Before 1945	353	4	1.1
	Total	4126	114	2.8

Table 14

Distribution of HI titers for A/Taiwan/86 of students and permanent party who did not have influenza in sera collected before or after the influenza epidemic

Students		No. of Persons	Cumulative percent with HI titer of: <8	8	16	32	64	128	256	512	1024
Pre-epidemic	11/2-12/10	25	28	72	60	44	32	12	8	-	-
Post-epidemic	2/12-5/7	25	4	96	88	68	52	32	24	16	11
Permanent Party											
Pre-epidemic	11/2-12/4	21	38	62	33	29	24	10	-	-	-
Post-epidemic	2/17-5/17	21	38	62	53	29	10	10	5	-	-

Table 15

Comparison of sensitivity of three diagnostic tests

	Virus Isolation	H.I. Test A/Taiwan/86	C.F. Test A/Taiwan/86
Students	9/15	14/15	8/16
	60%	93%	53%
Permanent Party	42/62	92/62	39/62
	68%	84%	63%
Total	51/77	66/77	47/77
	66%	86%	61%

Table 16

Etiology of febrile upper respiratory infection at Lowry AFB, 1986-87

Diagnosis	No. of Cases	Percent of Cases
Influenza A	152	32.5
Strep. Pharyn.	63	13.5
Adenovirus	3	0.6
Chlamydia TWAR	1	.02
Unkown	248	53.7
	467	100.0